DIFFERENTIAL INTERACTION BETWEEN VIRUS AND HOST CELL IN DEVELOPING VERSUS MATURE MOUSE BRAIN DETERMINES SPREAD, RESTRICTED REPLICATION, CELL DEATH, PERSISTENCE AND AGE-RELATED VIRULENCE OF SEMLIKI FOREST VIRUS

K. Oliver, M. Scallan, H. Dyson and J. Fazakerley.
Department of Pathology, University of Cambridge, Cambridge, UK.

Many neurotropic virus infections demonstrate an age-related virulence. Increase in age at time of virus inoculation is most often accompanied by a sharp or progressive decrease in susceptibility. The cellular and molecular events underlying this change in susceptibility have been unclear. The age-related susceptibility to Semliki Forest virus (SFV) infection has been investigated in this study. Following intraperitoneal inoculation of SFV (an alphavirus of the *Togaviridae*), the virus replicates in the periphery and subsequently reaches the Central Nervous System (CNS). Several disease states can result, depending on mouse age and virus strain. The L10 strain is virulent in all age groups, while the A7(74) strain is virulent only in neonatal and suckling mice. Infection of mice with A7(74) before postnatal day 12 (P12) resulted in a lethal encephalitis, whereas all mice infected after P14 survived and virus replication was restricted and non-destructive. Outcome of infection appears not to be linked to maturity of specific immune responses, but to spread of virus around the CNS, which is dependent on neuronal maturity and changes ongoing in the developing postnatal brain. Complete viral replication and transmission of infection requires smooth membrane synthesis which is present in neurons undergoing axonogenesis and synaptogenesis, and is absent in mature neurons, but inducible in them by administration of gold compounds. We have investigated neuropathological changes in this system, and, using *in situ* hybridisation with ^{35}S- and digoxigenin-labelled riboprobes, have observed distinct age-related changes in the spread, regional and cellular distribution of the virus in the developing mouse CNS, particularly in cells of the cortex, hippocampus and cerebellum.

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